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Dendritic Oxazoline Ligands in Enantioselective Palladium-Catalyzed Allylic Alkylations

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First to fourth generation dendritic substituents based on 2,2-bis(hydroxymethyl)propionic acid and (1*R*,2*S*,5*R*)-menthoxyacetic acid were attached to 2-(hydroxymethyl)pyridinooxazoline and bis-[4-(hydroxymethyl)oxazoline] compounds. The new ligands obtained were assessed in palladium-catalyzed allylic alkylations. The first type of ligands exhibited enantioselectivity similar to that of a benzoyl ester derivative, whereas the latter type of ligands afforded products with higher selectivity than the analogous benzoyl ester. The activity of the dendritic catalysts decreased with increasing generation.

Introduction

Dendrimers and dendrons are currently being exploited for a variety of applications,[1] the use of chiral ligands with dendritic structures[2] in metal-catalyzed reactions constituting one example.[3] The major reason for the preparation of such catalysts comes from advantageous workup procedures, in that separation of the catalyst from the products conveniently can be performed by, e.g., precipitation or nanofiltration, thus allowing recovery and reuse of the catalysts. Dendritic catalysts can also be used in flow-through reactors where they are retained by a membrane.[4] In addition, properties superior to those of the monomeric ligands may be envisaged. Thus, the solubility of the catalysts may be modified, occasionally leading to enhanced reactivity of the dendritic catalysts.[5]

Different strategies have been employed in the design of chiral dendritic metal catalysts. The catalyst can consist of a dendrimer or dendron having the groups responsible for the coordination to the metal center attached either to the periphery of the system or at the focal point. In the first type of systems, proximity of catalytic sites may lead to cooperative effects, as observed by Jacobsen et al. in the Co-salen-catalyzed hydrolytic kinetic resolution of terminal epoxides,[6] but multiple functionalities at the periphery can also cause aggregation of catalytic sites and thereby loss of catalytic activity.[3,7] The second type of dendritic catalysts is expected to provide enhanced selectivity, in particular enhanced enantioselectivity, in catalytic reactions by providing a sterically demanding environment created by the dendritic substituent, although these expectations are not always met.[1] In both types of systems, chirality may reside in the dendrimer part of the molecule and/or in the ligand skeleton. Achiral ligands with chiral dendritic substituents have so far resulted in very low enantioselectivity,[5] whereas chiral ligands substituted with dendrons[8] or chiral ligands attached to the periphery of a dendritic structure[9] in a variety of examples have been shown to behave like the monomeric ligands or, in a few cases, even to give better performance. The activity and selectivity of the dendritic catalysts often deteriorate upon increasing the generation, however.[3b]

We have exploited the use of [2-(hydroxymethyl)-pyridino]oxazolines[10] as well as *O*-alkylated and *O*-

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benzoylated[11] derivatives in palladium-catalyzed allylic substitutions[12] of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate and found that the selectivity as well as the reactivity of the catalytic systems are highly dependent on the group bound to oxygen. As ester derivatives of the parent alcohol are conveniently obtained, we decided to study the influence of dendritic substituents on the catalytic performance of this type of ligands and of bis[4-(hydroxymethyl)oxazolines)]. To the best of our knowledge, only achiral dendritic catalysts have previously been used in palladium-catalyzed allylation reactions.[4a,d,13]

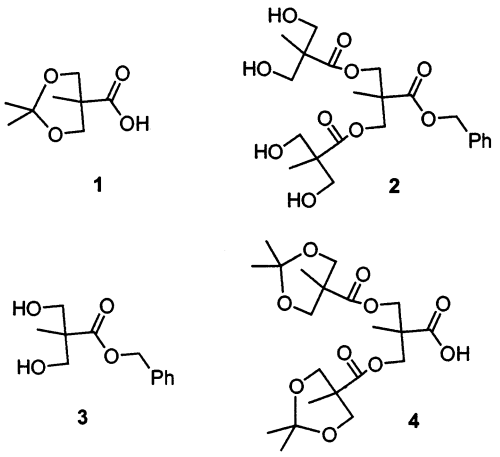
The synthesis of dendritic structures involves mainly two different approaches, leading to the same product: the convergent growth approach and the divergent growth approach. The approach of choice is related to the chemistry involved for the synthesis of the various building blocks used to construct a dendritic structure. In the convergent growth approach developed by Fréchet and Hawker, growth proceeds through coupling of chain ends to a focal molecule forming higher generation monodendrons.[14,15] Advantages such as the minimum number of coupling sites and simpler purification steps due to a larger difference in molecular weight of the product and the byproducts are main characteristics in the convergent growth approach. However, a major drawback of this approach is low yield in the higher generation monodendron coupling to a focal point due to steric hindrance. Moreover, loss of valuable monodendrons used in excess for the synthesis for the next generation monodendrons is disadvantageous.

In the divergent growth, monodendrons are grown layer by layer radially outward starting with the first generation monodendron. A disadvantage with this route is the high number of coupling sites. The number of sites is at least doubled for the formation of each new generation. Transformation of all chain ends is essential for the workup procedure and the formation of higher generation monodendrons. This is usually achieved by using a large excess of bulk reagent. The divergent growth has been described by, e.g., Tomalia et al.,[16] Newkome et al.,[17] and Fréchet et al.[15]

In this study a divergent growth was used for the preparation of acetonide-protected monodendrons based on bis-MPA as the repeating unit. The dendrons obtained were attached to pyridinooxazolines and bis(oxazolines),[18] and the resulting ligands assessed in Pd-catalyzed allylic alkylations.

Results and Discussion

Preparation of the Ligands. 2,2-Bis(hydroxymethyl)propionic acid was employed as a building block for the preparation of first, second, third, and fourth generation dendrons. Dendrons of the second and fourth generations of this kind have been synthesized previously by a double-stage convergent approach via intermediates **1**−**4**.[19,20] The disadvantage with this route is the loss of valuable second generation dendrons as they had to be used in excess for the synthesis of the fourth generation dendrons. Therefore a modified synthetic route was sought in order to minimize the amount of dendron loss. This was accomplished by the divergent approach with acetonide protected bis-MPA **(1)** as bulk material.



Acetonide-[G#3]-$CO_2CH_2C_6H_5$ (**5**) was synthesized in 87% yield from **1** and **2** using DPTS[21] and DCC. DOWEX, H^+ was used to cleave the acetonide, affording **6** in 86% yield. Acetonide-[G#4]-$CO_2CH_2C_6H_5$ (**7**) was obtained in 43% yield by a DPTS/DCC coupling between **6** and **1**. The removal of the benzyl group (H_2, Pd/C) was performed in 95% yield to give acetonide-[G#4]-COOH (**8**) (Scheme 1).[19]

A dendron with a chiral surface was synthesized from **3** and (1*R*,2*S*,5*R*)-menthoxyacetic acid, a commercially available and cheap chiral building block. The (1*R*,2*S*,5*R*)-menthoxyacetic acid-[G#1]-$CO_2CH_2C_6H_5$ (**9**) was obtained in 84% yield and gave, after removal of the benzyl group, (1*R*,2*S*,5*R*)-menthoxyacetic acid-[G#1]-CO_2H (**10**) in 97% yield (Scheme 2).

Dendrons containing free carboxylic acid groups and acetal protected alcohol functions (**1**, **4**, and **8**) were connected to (4′*R*)-2-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)pyridine (**11**)[22] or its enantiomer (*ent*-**11**) and to 2,2-bis[(4*S*,5*S*)-4-(hydroxymethyl)-5-phenyl-1,3-oxazolin-2-yl]propane (**12**) via ester formation using DPTS/DCC or DMAP/EDCI, to form (*S*)-**13a**-**b**, (*R*)-**13c**, and (*S*,*S*)-**14a**-**b**. Analogous couplings of the chiral den-

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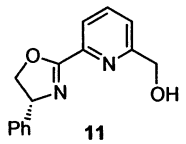
dron **10** gave (*R*)-**13d** and (*S*)-**13e** from **11** and *ent*-**11**, respectively, and (*S*,*S*)-**14c** and (*R*,*R*)-**14d** from **12** and *ent*-**12**, respectively.



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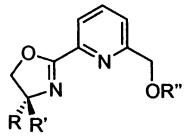
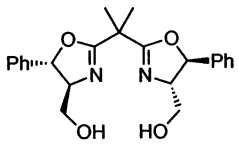


(*S*)-**13a** R=H, R'=Ph, R"=[G#1]-acetonide
(*S*)-**13b** R=H, R'=Ph, R"=[G#2]-acetonide
(*R*)-**13c** R=H, R'=Ph, R"=[G#4]-acetonide
(*R*)-**13d** R=H, R'=Ph, R"=[G#1]-(1R,2S,5R)-menthoxy acetic acid
(*S*)-**13e** R=H, R'=Ph, R"=[G#1]-(1R,2S,5R)-menthoxy acetic acid
(*R*)-**13f** R=H, R'=Ph, R"=COC_6H_5



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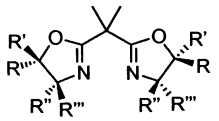

(*S*,*S*)-**14a** R=Ph, R'=H, R"=H, R'"=CH_2O-[G#1]-acetonide
(*S*,*S*)-**14b** R=Ph, R'=H, R"=H, R'"=CH_2O [G#4]-acetonide
(*S*,*S*)-**14c** R=Ph, R'=H, R"=H, R'"=CH_2O-[G#1]-(1R,2S,5R)-menthoxy acetic acid
(*R*,*R*)-**14d** R=Ph, R'=H, R"=H, R'"=CH_2O-[G#1]-(1R,2S,5R)-menthoxy acetic acid
(*S*,*S*)-**14e** R=Ph, R'=H, R"=H, R'"=$CH_2OCOC_6H_5$

Catalytic Reactions. Ligands (*S*)-**13a**,**b**, (*R*)-**13c**,**d**, (*S*)-**13e**, (*S*,*S*)-**14a**−**c**, and (*R*,*R*)-**14d** were assessed in palladium-catalyzed substitutions of *rac*-(*E*)-1,3-diphenylpropenyl acetate with malonate using bis[(π-allyl)-palladium chloride] as the palladium source in the presence of BSA and KOAc.[23] The results were compared to those obtained using benzoyl ester ligands (*R*)-**13f** and (*S*,*S*)-**14e**. In the pyridinooxazoline series of ligands with achiral dendritic wedges ((*S*)-**13a**,**b** and (*R*)-**13c**), the stereoselectivity achieved using the dendritic catalysts was similar to that observed using benzoyl ester (*R*)-**13f**, and the yields and reaction times required for full conversion were about the same for the different types of catalysts (Table 1).[24] However, we were pleased to observe that use of ligands (*S*,*S*)-**14a** and (*S*,*S*)-**14b** resulted in high enantioselectivity (88 and 92% ee, respectively), considerably higher than that using the benzoyl ester (*S*,*S*)-**14e** (81% ee). The reaction times and the yields varied considerably in the bis(oxazoline) series of ligands. Use of the benzoyl ester (*S*,*S*)-**14e** resulted in

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TABLE 1. Enantioselective Allylic Alkylations with Ligands 13 and 14

ligand	reaction time, h	yield, %	ee, %, product
(*S*)-**13a**	96	100	80 (*S*)
(*S*)-**13b**	96	100	78 (*S*)
(*R*)-**13c**	96	67−95	76 (*R*)
(*R*)-**13d**	96	100	79 (*R*)
(*R*)-**13f**[11]	96	76−98	77 (*R*)[11]
(*S*,*S*)-**14a**	48	89	92 (*S*)
(*S*,*S*)-**14b**	96	10	88 (*S*)
(*S*,*S*)-**14c**	96	100	94 (*S*)
(*S*,*S*)-**14e**	24	83	81 (*S*)

83% yield of product after 24 h, and reaction employing ligand (*S*,*S*)-**14a** afforded 89% yield within 48 h whereas the ligand substituted with forth generation dendrons ((*S*,*S*)-**14b**) exhibited low reactivity, yielding merely 10% of product after a reaction time of 96 h. Contrary to expectations,[25] high enantioselectivity was thus achieved employing polar dendritic wedges, the polar substituents probably not competing for catalytic sites.

The introduction of a chiral dendritic substituent on the alcohol **11** had no effect on the enantioselectivity, the two diastereomers (*R*)-**13d** and (*S*)-**13e** both resulting in 79% ee. This is in analogy to previous observations using TADDOL ligands substituted with chiral dendritic wedges.[25] In contrast, substitution of **12** with the same chiral dendron yielded catalyst (*S*,*S*)-**14c**, which exhibited somewhat higher stereoselectivity (94% ee) than the bis(oxazoline) ligands carrying achiral dendrons. The chirality of the substituents did not, however, influence the selectivity of the catalytic reaction, as the diastereomeric ligand (*R*,*R*)-**14d**, obtained from *ent*-**12**, afforded a product with the same enantioselectivity. To achieve full conversion in reactions employing the ligands with the chiral dendrons, extended reaction times were required.

Dendritic substituents thus have different effects on the two classes of ligands. The lack of influence in the reactions using the pyridinooxazoline ligands may be explained by the long distance between the dendritic substituent and the catalytic center and/or the too high flexibility of that system. In the bis(oxazoline) series of ligands the dendritic wedges seem to be situated close enough to the catalytic center to have an effect on the stereoselectivity and the reactivity, leading to increased stereoselectivity but, unfortunately, to a decrease in activity of the catalytic system.

Conclusions. Depending on the structure of the parent ligand, the attachment of dendritic substituents may either exert little effect on the stereoselectivity and the activity of the catalytic process or have a beneficial influence on the selectivity, but at the same time a detrimental effect on the reactivity of the catalytic system.

Experimental Section

Materials and Techniques. 2,2-Bis(hydroxymethyl)propionic acid (bis-MPA) was obtained commercially. Compounds **1**−**4** were synthesized according to a procedure described by Hult et al.[19] DPTS was synthesized as described by Moore and Stupp.[21] (1*S*,2*S*)-2-Amino-1-phenylpropane-1,3-diol was

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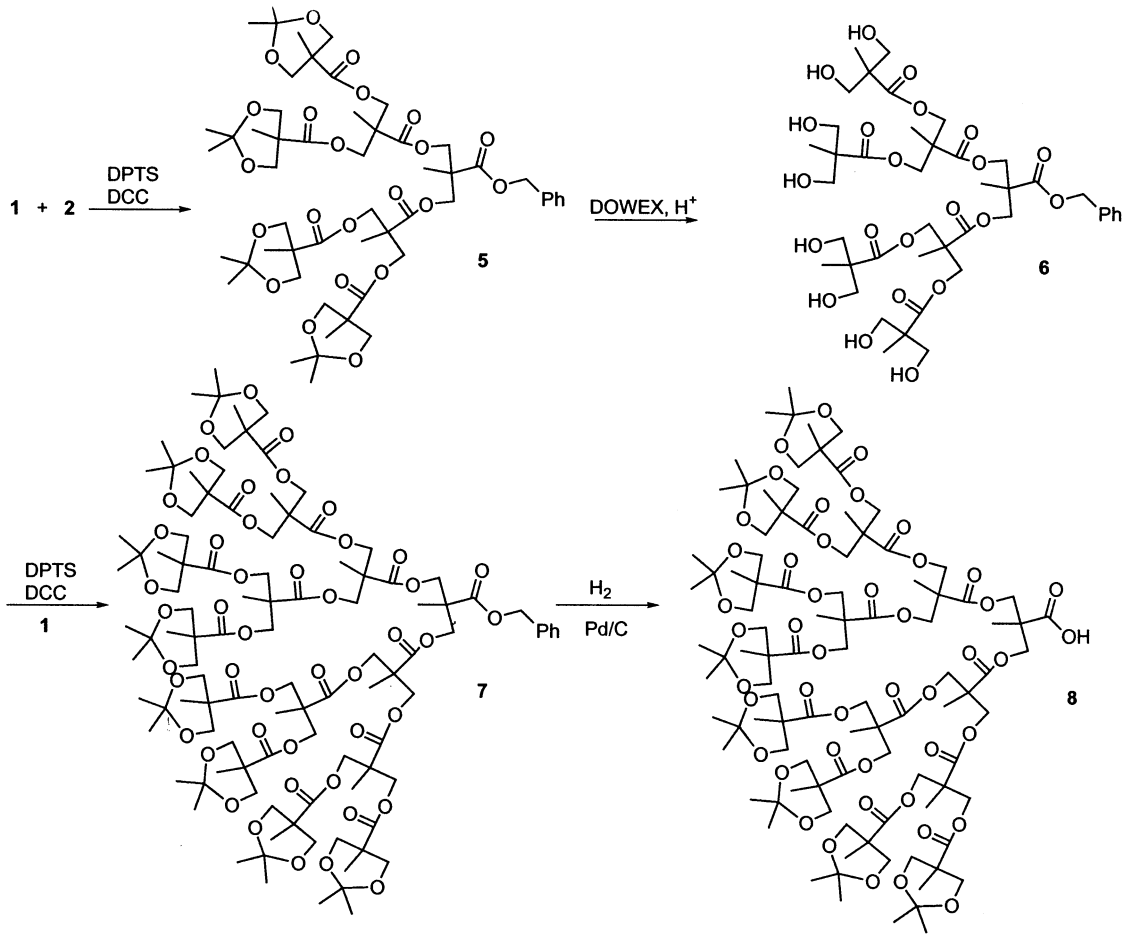
SCHEME 1



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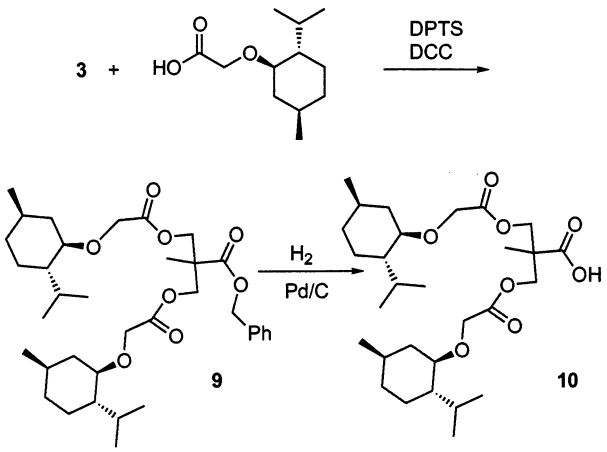

obtained commercially. 2,2-Bis[(4*S*,5*S*)-4-hydroxymethyl-5-phenyl-1,3-oxazolin-2-yl]propane was obtained according to a described procedure.[26] CH_2Cl_2 was distilled from CaH_2 before use. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400.1 and 100.6 MHz, respectively, in $CDCl_3$, unless otherwise stated. The solvent signal was used as internal standard. All purifications were performed by medium-pressure liquid chromatography or by flash chromatography. Enantiomeric excesses were determined by HPLC using a chiral column (Chiralcel OD-H, 0.5 mL/min, 99:1 hexane:propan-2-ol).

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Acetonide-[G#3]-$CO_2CH_2C_6H_5$ (5). DPTS (0.26 g, 0.87 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (1.45 g, 7.01 mmol) were added to a solution of **2** (0.50 g, 1.10 mmol) and **1** (0.92 g, 5.26 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 72 h and the DCC-urea was filtered off in a glass filter and washed with small amounts of CH_2Cl_2. The solvent was evaporated and the crude product was purified by liquid chromatography on silica gel using a gradient from pure hexane to 80:20 ethyl acetate:hexane to give **5** as a colorless viscous oil (1.03 g, 87%). TLC (silica) hexane:ethyl acetate 40:60, R_f 0.4; ^{1}H NMR δ 1.12 (s, 12H), 1.18 (s, 6H), 1.26 (s, 3H), 1.33 (s, 12H), 1.39 (s, 12H), 3.59 (d, 8H, J = 12.2 Hz), 4.12 (d, 8H, J = 12.2 Hz), 4.15−4.29 (m, 12H), 5.14 (s, 2H), 7.28−7.34 (m, 5H);^{13}C NMR δ 17.54, 18.48, 22.07, 25.10, 25.39, 42.01, 46.68, 46.79, 64.87, 65.66, 65.89, 65.94, 65.99, 67.16, 67,93, 98.07, 128.43, 128.50, 128.66, 135.35, 171.80, 171.90, 173.44.

(HO)$_8$-[G#3]-$CO_2CH_2C_6H_5$ (6). Compound **5** (0.84 g, 0.78 mmol) was dissolved in MeOH (20 mL) and one teaspoon of DOWEX, H^+ resin was added. The mixture was allowed to react for 3 h at 50 °C to give **6** as white crystals (0.63 g, 86%). ^{1}H NMR (DMSO) δ 1.01 (s, 12H), 1.10 (s, 6H), 1.21 (s, 3H), 3.34−3.49 (m, 8H), 4.05−4.10 (m, 8H), 4.18, 4.24 (AB system, 4H, J = 11.0 Hz), 4.66 (app t, 8H, J = 5.3 Hz), 5.18 (s, 2H), 7.35 (m, 5H); ^{13}C NMR (DMSO) δ 16.72, 17.03, 17.07, 46.27, 46.33, 50.3, 63.72, 64.52, 65.82, 66.41, 127.94, 128.23, 128.55, 135.70, 171.88, 171.95, 174.11. The hydroxy protons (8H) were not observed.

Acetonide-[G#4]-$CO_2CH_2C_6H_5$ (7). This compound was prepared and purified according to the procedure described for **5**, starting from DPTS (0.63 g, 2.13 mmol), DCC (3.50 g, 17.0 mmol), **6** (1.00 g, 1.09 mmol), **1** (2.22 g, 12.8 mmol), and

CH_2Cl_2 (15 mL) to give **7** as a colorless viscous oil (1.0 g, 43%). Spectral data were in accordance with those published.[19]

(1*R*,2*S*,5*R*)-(2-Isopropyl-5-methylcyclohexyl-1-oxy)acetic-[G#1]-COOCH$_2$C$_6$H$_5$ (9). (1*R*,2*S*,5*R*)-Menthoxyacetic acid (2.30 g, 10.7 mmol), benzyl-2,2-bis(methylol)propionate **3** (1.00 g, 4.46 mmol), and DPTS (0.52 g, 1.79 mmol) were mixed in CH_2Cl_2 (20 mL) and DCC (3.00 g, 13.4 mmol) was added. The mixture was stirred for 18 h at room temperature, and the DCC-urea was filtered off in a glass filter and washed with small amounts of CH_2Cl_2. The solvent was evaporated and the crude product was purified by liquid chromatography on silica gel, using a gradient from pure hexane to 20:80 ethyl acetate: hexane to give **9** as a colorless viscous oil (2.31 g, 84%). TLC (silica) ethyl acetate:hexane 20:80, R_f 0.6; ^{1}H NMR δ 0.71−0.93 (m, 24H), 1.19−1.26 (m, 7H), 1.58−1.65 (m, 4H), 1.98−2.03 (m, 2H), 2.20−2.27 (m, 2H), 3.10 (dt, 2H, J = 10.7 and 4.2 Hz), 3.96, 4.03 (AB system, 2H, J = 16.3 Hz), 3.97, 4.05 (AB system, 2H, J = 16.3 Hz), 4.25−4.30 (m, 4H), 5.02 (s, 2H), 7.30−7.36 (m, 5H);^{13}C NMR δ 16.25, 17.70, 22.25, 23.26, 25.47, 31.46, 34.36, 39.93, 46.35, 48.04, 65.37, 65.40, 65.62, 66.84, 80.32, 128.13, 128.37, 128.57, 135.51, 170.30, 172.24.

(1*R*,2*S*,5*R*)-(2-Isopropyl-5-methylcyclohexyl-1-oxy)acetic-[G#1]-COOH (10). Pd/C (10%) (0.23 g) was added to a solution of **9** (2.3 g, 3.7 mmol) in ethyl acetate (50 mL). The mixture was stirred vigorously and the flask was evacuated and filled with H_2 (g). After 18 h the reaction was complete. The Pd/C was filtered through a glass filter and washed with small amounts of ethyl acetate. The solvent was evaporated to give **10** as a colorless oil (1.9 g, 97%); $[\alpha]^{25}_D$ −65 (*c* 0.31, CH_2Cl_2); ^{1}H NMR δ 0.70−0.93 (m, 24H), 1.19−1.25 (m, 7H), 1.56−1.62 (m, 4H), 1.92−2.04 (m, 2H), 2.19−2.24 (m, 2H), 3.12 (dt, 2H, J = 10.6 and 4.1 Hz), 4.04, 4.12 (AB system, 4H, J = 16.3 Hz), 4.22−4.31 (m, 4H), 10.9 (br s, 1H);^{13}C NMR δ 16.15, 17.67, 20.82, 22.14, 23.17, 25.38, 31.37, 34.27, 39.84, 45.96, 47.96, 64.94, 64.98, 65.63, 80.34, 170.24, 177.71.

(4′*S*)-2-(4′,5′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)pyridine ((*ent*)-11). This compound was synthesized from (*S*)-phenylglycinol using the procedure published for (4′*R*)-2-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)-pyridine. The spectral data were identical with those of the enantiomer.[22] $[\alpha]^{20}_D$ −48.7 (*c* 0.27, CH_2Cl_2).

(4′*S*)-2-(Acetonide-[G#1]-COOCH$_2$)-6-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)pyridine ((*S*)-13a). (*S*)-**13a** was prepared according to the procedure described for **5**, starting from DPTS (5 mg, 17 μmol), DCC (20 mg, 0.099 mmol), (*S*)-**11** (22 mg, 0.083 mmol), **1** (22 mg, 0.091 mmol), and CH_2Cl_2 (1 mL). The mixture was stirred for 24 h at room temperature and purified by chromatography as described for **5** using a gradient from pure hexane to 60:40 ethyl acetate:hexane to give (*S*)-**13a** as a colorless viscous oil (18 mg, 64%): $[\alpha]_D^{20}$ −30.5 (*c* 0.90, CH_2Cl_2); ^{1}H NMR δ 1.23 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 3.69 (d, 2H, J = 11.9 Hz), 4.13 (d, 2H, J = 11.9 Hz), 4.39 (app t, 1H, J = 8.5 Hz), 4.89 (dd, 1H, J = 10.2 and 8.6 Hz), 5.39−5.47 (m, 3H), 7.26−7.40 (m, 5H), 7.57 (d, 1H, J = 7.8 Hz), 7.81 (app t, 1H, J = 7.8 Hz), 8.09 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 18.56, 21.86, 25.58, 42.11, 66.20, 66.73, 70.37, 75.49, 98.22, 123.11, 123.39, 126.87, 127.81, 128.84, 137.53, 141.79, 146.25, 156.61, 163.67, 173.85. HRMS (EI) calcd for $C_{23}H_{26}N_2O_5$ 410.1842, found 411.1899 (MH^+).

(4′*S*)-2-(Acetonide-[G#2]-COOCH$_2$)-6-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)pyridine ((*S*)-13b). (*S*)-**13b** was prepared according to the procedure described for **5**, starting from DPTS (23 mg, 79 μmol), DCC (130 mg, 0.63 mmol), *ent*-**11** (0.10 g, 0.39 mmol), **4** (0.21 g, 0.39 mmol), and CH_2Cl_2 (0.5 mL). The mixture was stirred for 48 h at room temperature. The thick mixture was filtered through Celite and the product was eluted from the Celite with diethyl ether. The solvent was evaporated and the product was purified by flash chromatography on silica gel with hexane:ethyl acetate 1:1 as eluent to give (*S*)-**13b** as a colorless oil (0.10 g, 38%). $[\alpha]_D^{20}$ −23.4 (*c* 0.85, CH_2Cl_2); ^{1}H NMR δ 1.11 (s, 6H), 1.33 (s, 6H), 1.36 (s, 3H), 1.40 (s, 6H), 3.59 (d, 4H, J = 11.8 Hz), 4.13 (d, 4H, J = 11.8 Hz), 4.36−4.43 (m, 5H), 4.90 (dd, 1H, J = 10.3 and 8.6 Hz), 5.39 (s, 2H), 5.43 (dd, 1H, J = 10.3 and 8.6 Hz), 7.27−7.39 (m, 5H), 7.49 (d, 1H, J = 7.7 Hz), 7.82 (app t, 1H, J = 7.8 Hz), 8.11 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ 17.76, 18.47, 21.96, 25,22, 42.08, 46.95, 65.27, 65.93, 65.98, 67.31, 70.34, 75.46, 98.10, 123.44, 123.59, 126.82, 127.78, 128.80, 137.58, 141.69, 146.39, 155, 87, 163. 52, 172.12, 173.54. HRMS (EI) calcd for $C_{36}H_{46}N_2O_{11}$ 682.3102, found 683.3186 (MH^+).

(4′*R*)-2-(Acetonide-[G#4]-COOCH$_2$)-6-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)pyridine ((*R*)-13c). (*R*)-**13c** was prepared according to the procedure described for **5**, starting from DCC (0.35 mg, 0.118 mmol), DPTS (39 mg, 19 μmol), **11** (30 mg, 0.118 mmol), **8** (0.29 g, 0.142 mmol), and CH_2Cl_2 (5 mL). The mixture was stirred for 48 h at room temperature and purified as described for **5** using a gradient from pure hexane to 80:20 ethyl acetate:hexane to give (*R*)-**13c** as a colorless viscous oil (82 mg, 30%). TLC (silica) ethyl acetate:hexane 80:20, R_f 0.3; $[\alpha]^{20}_D$ +4.9 (*c* 1.1, CH_2Cl_2); ^{1}H NMR δ 1.11 (s, 24H), 1.21 (s, 6H), 1.24 (s, 12H), 1.31 (s, 24H), 1.34 (s, 3H), 1.38 (s, 24H), 3.60 (d, 16H, J = 11.8 Hz), 4.13 (d, 16H, J = 11.8 Hz), 4.15−4.40 (m, 29H), 4.89 (dd, 1H, J = 10.2 and 8.7 Hz), 5.36 (s, 2H), 5.44 (app t, 1H, J = 9.4 Hz), 7.27−7.38 (m, 5H), 7.52 (d, 1H, J = 7.6 Hz), 7.87 (app t, 1H, J = 7.8 Hz), 8.11 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 17.57, 17.78, 18.57, 22.06, 25.35, 42.11, 46.78, 46.82, 46.90, 64.87, 65.53, 65.99, 66.04, 66.35, 67.61, 70.37, 75.55, 98.20, 123.76, 123.82, 126.92, 127.89, 128.90, 137.92, 141.77, 146.48, 155.74, 163.62, 171.52, 171.61, 171.91, 173.56. Some of the quaternary carbon atoms were not visible.

(4′*R*,1″*R*,2″*S*,5″*R*)-2-(4′,5′-Dihydro-4′-phenyl-2′-oxazolyl)-6-[(2″-isopropyl-5″-methylcyclohexyl-1″-oxy)acetic-[G#1]-COOCH$_2$]pyridine ((*R*)-13d). (*R*)-**13d** was prepared according to the procedure described for **5**, starting from DPTS (12 mg, 40 μmol), DCC (57 mg, 0.28 mmol), **11** (50 mg, 0.197 mmol), **10** (0.114 g, 0.216 mmol), and CH_2Cl_2 (5 mL). The mixture was stirred for 48 h at room temperature and purified as described for **5** using a gradient from pure hexane to 60:40 hexane:ethyl acetate to give (*R*)-**13d** as a colorless viscous oil (24 mg, 16%). TLC (silica) hexane:ethyl acetate 60:40, R_f 0.5; $[\alpha]^{20}_D$ −34,3 (*c* 0.59, CH_2Cl_2);^{1}H NMR δ 0.76−1.0 (m, 24H), 1.20−1.40 (m, 7H), 1.55−1.65 (m, 4H), 1.94−2.05 (m, 2H), 2.24 (m, 2H), 3.12 (dt, 2H, J = 10.6 and 4.2 Hz), 4.04, 4.11 (AB system, 2H, J = 16.3 Hz), 4.05, 4.13 (AB system, 2H, J = 16.3 Hz), 4.30−4.43 (m, 5H), 4.90(dd, 1H, J = 10.3 and 8.8 Hz), 5.38 (s, 2H), 5.44 (app t, 1H, J = 9.4 Hz), 7.27−35 (m, 5H), 7.45 (d, 1H, J = 7.8 Hz), 7.82 (app t, 1H, J = 7.8 Hz), 8.11 (d, 1H, J = 7.8 Hz);^{13}C NMR δ 16.38, 17.97, 21.08, 22.41, 23.35, 25.60, 31.59, 34.48, 40.06, 46.58, 48.17, 65.46, 65.84, 67.43, 70.47, 75.64, 80.50, 123.50, 123.75, 126.98, 127.95, 128.96, 137.73, 141.79, 146.49, 155.97, 163.63, 170.50, 172.13. HRMS (EI) calcd for $C_{44}H_{62}N_2O_9$ 762.4455, found 763.4504 (MH^+).

(4′*S*,1″*R*,2″*S*,5″*R*)-2-(4′,5′-Dihydro-4′-phenyl-2′-oxazolyl)-6-[(2″-isopropyl-5″-methylcyclohexyl-1″-oxy)acetic-[G#1]-COOCH$_2$]pyridine ((*S*)-13e). (*S*)-**13e** was prepared according to the procedure described for **5**, starting from DPTS (12 mg, 40 μmol), DCC (57 mg, 0.28 mmol), (*S*)-**11** (50 mg, 0.20 mmol), **10** (0.114 g, 0.22 mmol), and CH_2Cl_2 (5 mL). The mixture was stirred for 72 h at room temperature and purified as described for **5** using a gradient from pure hexane to 40:60 ethyl acetate: hexane to give (*S*)-**13e** as a colorless viscous oil (46 mg, 31%). TLC (silica) hexane:ethyl acetate 40:60, R_f 0.4; $[\alpha]_D^{20}$ −71,8 (*c* 1.2, CH_2Cl_2); ^{1}H NMR δ 0.76−1.0 (m, 24H), 1.20−1.40 (m, 7H), 1.55−1.65 (m, 4H), 1.98−2.07 (m, 2H), 2.18−2.28 (m, 2H), 3.12 (dt, 2H, J = 10.6 and 4.1 Hz), 4.026, 4.12 (AB system, 2H, J = 16.3 Hz), 4.034, 4.11 (AB system, 2H, J = 16.3 Hz), 4.30−4.45 (m, 5H), 4.89 (dd, 1H, J = 10.3 and 8.6 Hz), 5.38 (s, 2H), 5.44 (dd, 1H, J = 10.2 and 8.6 Hz), 7.27−35 (m, 5H), 7.46 (d, 1H, J = 7.7 Hz), 7.82 (app t, 1H, J = 7.8 Hz), 8.11 (d, 1H, J = 7.4 Hz);^{13}C NMR δ 16.41, 17.95, 21.06, 22.39, 23.40, 25.63, 31.60, 34.50, 40.09, 46.62, 48.21, 65.47, 65.87, 67.42, 70.45, 75.62, 80.54, 123.50, 123.74, 126.95, 127.93, 128.95, 137.69, 141.79, 146.50, 156.00, 163.67, 170.46, 172.12.

(4′*S*,5′*S*)-2,2-Bis[4′,5′-dihydro-4′-(acetonide-[G#1]-$COOCH_2$)-5′-phenyl-2′-oxazolyl]propane ((*S*,*S*)-14a). This compound was prepared according to the procedure described for **5**, starting from DPTS (15 mg, 0.005 mmol), DCC (78 mg, 0.38 mmol), (*S*,*S*)-**12** (50 mg, 0.13 mmol), **1** (53 mg, 0.30 mmol), and CH_2Cl_2 (2 mL). The mixture was stirred for 48 h at room temperature and purified as described for **5** using a gradient from pure hexane to 60:40 ethyl acetate:hexane to give (*S*,*S*)-**14a** as a viscous oil (56 mg, 63%). TLC (silica) hexane:ethyl acetate 40:60, R_f 0.70; $[\alpha]^{20}_D$ −25.6 (*c* 0.43, CH_2Cl_2);^{1}H NMR δ 1.09 (s, 6H), 1.34 (s, 6H), 1.39 (s, 6H), 1.68 (s, 6H), 3.56 (dd, 4H, J = 12.1 and 2.0 Hz), 4.12 (d, 4H, J = 11.8 Hz), 4.20−4.30 (m, 4H), 4.44, 4.47 (AB system, 2H, J = 5.4 Hz), 5.27(d, 2H, J = 6.5 Hz), 7.25−7.30 (br s, 10H);^{13}C NMR δ 18.64, 22.80, 24.73, 25.06, 34.03, 39.31, 42.11, 65.21, 66.01, 73.84, 83.97, 98.20, 126.06, 128.65, 128.95, 140.18, 170.23, 174.21.

(4′*S*,5′*S*)-2,2-Bis[4′,5′-dihydro-4′-(acetonide-[G#4]-$COOCH_2$)-5′-phenyl-2′-oxazolyl]propane ((*S*,*S*)-14b). This compound was prepared according to the procedure described for **5**, starting from DPTS (6 mg, 2 μmol), DCC (31 mg, 0.15 mmol), (*S*,*S*)-**12** (20 mg, 51 μmol), **8** (0.253 g, 0.12 mmol), and CH_2Cl_2 (1 mL). The mixture was stirred for 72 h at room temperature and purified as described for **5** using a gradient from pure hexane to 100% ethyl acetate to give (*S*,*S*)-**14b** as a colorless viscous oil (0.100 g, 44%). TLC (silica) hexane:ethyl acetate 20:80, R_f 0.6; $[\alpha]_D^{20}$ −0.44 (*c* 4.8, CH_2Cl_2); ^{1}H NMR δ 1.14 (s, 48H), 1.14 (s, 6H), 1.27 (s, 24H), 1.28 (s, 12H), 1.34 (s, 48H), 1.41 (s, 48H), 1.67 (s, 6H), 3.61 (d, 32H, J = 11.6 Hz), 4.16 (d, 32H, J = 11.6 Hz), 4.16−4.40 (m, 60H), 4.45 (dd, 2H, J = 11.0 and 3.9 Hz), 5.30 (d, 2H, J = 7.3 Hz), 7.26−7.32 (m, 10H); ^{13}C NMR δ 17.38, 17.63, 17.79, 18.62, 22.22, 24.88, 25.55, 39.25, 42.13, 46.46, 46.77, 46.92, 64.88, 65.47, 66.00, 66.06, 98.18, 126.30, 128.96, 139.83, 170.20, 171.20, 171.51, 171.90, 173.54. Some of the carbon atoms from the bis(oxazoline) structure were not visible due to a low relative concentration.

(4′*S*,5′*S*,1″*R*,2″*S*,5″*R*)-2,2-Bis[4′,5′-dihydro-4′-[(2″-isopropyl-5″-methylcyclohexyl-1″-oxy)acetic-[G#1]-$COOCH_2$]-5′-phenyl-2′-oxazolyl]propane ((*S*,*S*)-14c). DMAP (14 mg, 0.12 mmol) and EDCI (67 mg, 0.35 mmol) were added to a solution of (*S*,*S*)-**12** (46 mg, 0.12 mmol) and **10** (0.16 g, 0.30 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 24 h at room temperature and diluted with CH_2Cl_2. After extraction with 10% $NaHSO_4$ and brine the solvent was evaporated and the product was purified by liquid chromatography on silica gel, using a gradient from pure hexane to 60:40 ethyl acetate: hexane to give (*S*,*S*)-**14c** as a colorless viscous oil (40 mg, 24%). TLC ethyl acetate:hexane 60:40, R_f 0.7; $[\alpha]^{20}_D$ −68.6 (*c* 0.26, CH_2Cl_2);^{1}H NMR δ 0.76−1.0 (m, 48H), 1.13 (s, 6H), 1.20−1.40 (m, 8H), 1.55−1.67 (m, 14H), 1.98−2.02 (m, 4H), 2.20−2.30 (m, 4H), 3.10 (dt, 4H, J = 10.5 and 4.0 Hz), 3.95−4.28 (m, 20H), 4.42 (d, 2H, J = 8.3 Hz), 5.26 (d, 2H, J = 6.8 Hz), 7.25−7.30 (m, 10H);^{13}C NMR δ 16.36, 17.67, 21.08, 22.39, 23.34, 24.77, 25.57, 31.57, 34.46, 39.29, 40.01, 46.52, 48.14, 65.24, 65.80, 73.67, 80.42, 80.49, 84.10, 126.05, 128.72, 129.00, 140.03, 170.25, 170.39, 172.34. HRMS (EI) calcd for $C_{81}H_{122}N_2O_{18}$ 1410.8693, found 1411.8779 (MH^+).

(4′*R*,5′*R*,1″*R*,2″*S*,5″*R*)-2,2-Bis[4′,5′-dihydro-4′-[(2″-isopropyl-5″-methylcyclohexyl-1″-oxy)acetic-[G#1]-$COOCH_2$]-5′-phenyl-2′-oxazolyl]propane ((*R*,*R*)-14d). This compound was prepared from (*R*,*R*)-**12** (80 mg, 0.20 mmol) and **10** (329 mg, 0.625 mmol) using a procedure similar to that used for the preparation of (***S*,*S***)-**14c**: colorless oil (51 mg, 18%); $[\alpha]^{20}_D$ −32 (*c* 0.24, CH_2Cl_2); ^{1}H NMR δ 0.74−1.0 (m, 48H), 1.12 (s, 6H), 1.22−1.38 (m, 8H), 1.55−1.66 (m, 14H), 1.97−2.02 (m, 4H), 2.18−2.29 (m, 4H), 3.10 (dt, 4H, J = 10.5 and 3.7 Hz), 3.95−4.27 (m, 20H), 4.42 (d, 2H, J = 10.3 Hz), 5.26 (d, 2H, J = 6.6 Hz), 7.25−7.30 (m, 10H); ^{13}C NMR δ 16.25, 17.52, 20.90, 22.23, 23.25, 24.63, 25.46, 31.42, 34.34, 39.15, 39.90, 46.41, 48.02, 65.14, 65.17, 65.64, 65.72, 73.58, 77.20, 80.33, 83.94, 125.87, 128.56, 128.83, 139.95, 170.09, 170.21, 172.18.

2,2-Bis[(4*S*,5*S*)-4-methylphenylcarboxy-5-phenyl-1,3-oxazolin-2-yl]propane ((*S*,*S*)-14e). A solution of (*S*,*S*)-**12** (197 mg, 0.50 mmol), benzoic acid (183 mg, 1.50 mmol), EDCI (385 mg, 2.01 mmol), and DMAP (12.2 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was stirred for 48 h at room temperature. The reaction mixture was poured into 0.025 M HCl and extracted with ethyl acetate. The organic layer was separated, washed with water, saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (50:50 hexane:ethyl acetate) to afford (*S*,*S*)-**14e** as a viscous oil that solidified upon cooling to 5 °C (300 mg, quantitative): mp 84 °C. $[\alpha]_D^{20}$ −71 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.64 (s, 6H), 4.31 (m, 2H), 4.47 (m, 4H), 5.29 (d, 2H, J = 6.7 Hz), 7.19 (m, 10H), 7.27 (m, 4H), 7.44 (m, 2H), 7.91 (m, 4H); ^{13}C NMR δ 170.6, 166.7, 140.5, 133.5, 130.1, 129.2, 128.9, 128.8, 126.2, 84.5, 74.2, 66.0, 39.6, 25.2; HRMS (EI) calcd for $C_{37}H_{34}N_2O_6$ 602.2417, found 603.2496 (MH^+); Anal. Calcd for $C_{37}H_{34}N_2O_6$: C 73.74, H 5.69, N 4.65. Found C 73.58, H 5.84, N 4.45.

General Procedure for the Catalytic Reactions. Ligand (0.029 mmol, 6 mol %) and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (3.5 mg, 9.6 μmol, 2 mol %) were dissolved in CH_2Cl_2 (1 mL) under dry conditions. The solution was degassed at −78 °C and put under nitrogen atmosphere before the reaction vessel was sealed. The reaction mixture was stirred for 2 h at 50 °C and then cooled to −78 °C. 1,3-(*E*)-Diphenyl-2-propenyl acetate (121 mg, 0.480 mmol) was transferred to the reaction vessel with CH_2Cl_2 (1 mL). *N*,*O*-Bis(trimethylsilyl)acetamide (292 mg, 1.44 mmol), dimethyl malonate (142 mg, 1.07 mmol), and KOAc (2−3 mg, ∼0.025 mmol, ∼5 mol %) were added. The reaction vessel was degassed at −78 °C under nitrogen. The mixture was stirred at room temperature for the appropriate time before saturated aqueous NH_4Cl was added and the mixture was extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated. Residual BSA and dimethyl malonate were removed with short path distillation under vacuum at 90 °C.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **5**, **6**, **9**, **10**, (*S*)-**13a**−**c**, (*R*)-**13d**, (*S*)-**13e**, (*S*,*S*)-**14a**−**c**, and (*R*,*R*)-**14d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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